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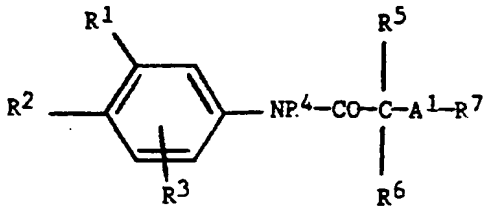
## (54) Substituted anilides having antiandrogenic properties.

(57) An acylanilide of the formula:-



wherein $R^1$ or $R^2$ which may be the same or different, each is an electron-withdrawing substituent, alkylthio or phenylthio or $R^1$ is hydrogen, alkyl or alkoxy;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl, or is joined to $R^5$ as stated below:
wherein $R^5$ is hydrogen, hydroxy, alkoxy or acyloxy, or is joined to $R^4$ to form an oxycarbonyl group;
wherein $R^6$ is alkyl or halogenoalkyl, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene, alkenylene or alkynylene;
wherein $A^2$ is alkylene, alkenylene or alkynylene;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl, substituted phenyl, naphthyl or 5-or 6-membered saturated or unsaturated heterocyclic.
The compounds possess antiandrogenic properties and some of the compounds also possess progestational or antiprogestational activity.

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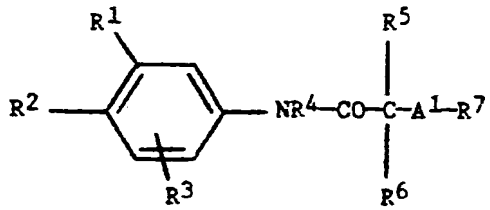
# AMIDE DERIVATIVES

This invention relates to new amide derivatives and more particularly it relates to novel acylanilides which possess antiandrogenic properties.

According to the invention there is provided an acylanilide of the formula:



wherein $R^1$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^2$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to $R^5$ as stated below;
wherein $R^5$ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to $R^4$ to form an oxycarbonyl group such that together with the -N-CO-C-part of the molecule it forms an oxazolidinedione group;
wherein $R^6$ is alkyl or halogenoalkyl each of up to 4 carbon atoms, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms; wherein $A^2$ is alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; naphthyl; 5-or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents.

It will be observed that the acylanilide derivative of the invention possesses an asymmetric carbon atom, namely the carbon atom which bears the substituents $R^5$ and $R^6$, and it can therefore exist in racemic and optically-active forms. It is to be understood that this invention encompasses the racemic form of the acylanilide derivative and any optically-active form which possesses antiandrogenic activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any antiandrogenic activity present in any of these forms may be determined.

A suitable value for $R^1$ or $R^4$ when it is alkyl, or for an alkyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by alkyl is, for example, methyl or ethyl.

A suitable value for $R^1$ when it is alkoxy or for an alkoxy substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for $R^1$ or $R^2$ when it is alkanoyl, or for an alkanoyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl substituted by alkanoyl is, for example, formyl or acetyl.

A suitable value for $R^1$ or $R^2$ when it is alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl, or for such a substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic bearing such a substituent is, for example, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for $R^3$ when it is halogen, or for a halogen substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by halogen, is fluoro, chloro, bromo or iodo.

$R^3$ is preferably hydrogen or chloro, especially hydrogen.

$R^4$ is preferably hydrogen.

A suitable value for an alkoxycarbonyl or N-alkylcarbamoyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl bearing such a substituent is, for example, methoxycarbonyl, ethoxycarbonyl or N-methylcarbamoyl.

A suitable value for $R^5$ when it is alkoxy is, for example, methoxy, ethoxy, propyloxy, n-butyloxy or decyloxy.

A suitable value for $R^5$ when it is acyloxy is, for example, alkanoyl or aroyl each of up to 15 carbon atoms, for example acetoxy, propionyloxy, decanoyloxy, dodecanoyloxy or benzoyloxy.

$R^5$ is preferably hydroxy.

A suitable value for $R^6$ when it is alkyl or halogenoalkyl is, for example, methyl, ethyl, n-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, chloromethyl, dichloromethyl or trichloromethyl. $R^6$ is preferably trifluoromethyl.

A suitable value for $A^1$ when it is alkylene is, for example, methylene, ethylene, trimethylene or tetramethylene.

A suitable value for $A^2$ when it is alkylene is, for example, methylene, ethylene, trimethylene, tetramethylene.

1-methylethylene ($-\overset{CH_3}{\underset{|}{CH}}-CH_2-$), 2-methylethylene ($-CH_2\overset{CH_3}{\underset{|}{CH}}-$) or

1,1,3-trimethylpropane-1,3-diyl ($-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2\overset{CH_3}{\underset{|}{CH}}-$).

A suitable value for $A^1$ or $A^2$ when it is alkenylene or alkynylene is, for example, vinylene (-CH=CH-), prop-1-enylene (-CH=CH-$CH_2$-), 2-methylprop-1-enylene

($-CH=\overset{CH_3}{\underset{|}{C}}-CH_2-$)

, ethynylene (-C≡C-), prop-1-ynylene (-C≡C-$CH_2$-) or prop-2-ynylene (-$CH_2$C≡C-).

A suitable value for $R^7$ or $R^8$ when it is heterocyclic is, for example, furyl, thienyl, pyrrolyl, pyridyl, imidazolyl, thiazolyl, thiadiazolyl, benzimidazolyl, indolyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or 1,2-dihydro-2-oxoquinolyl.

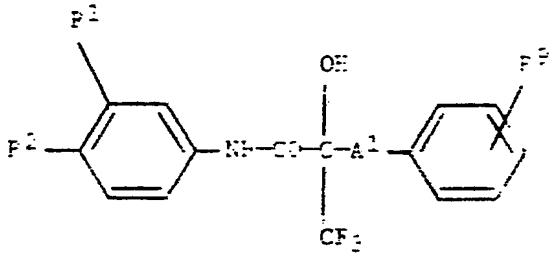
A preferred combination of values for $R^1$ and $R^2$ is as follows:-

| $R^1$ | $R^2$ |
|---|---|
| trifluoromethyl | nitro |
| trifluoromethyl | cyano |
| chloro | chloro |
| chloro | nitro |
| chloro | cyano |
| cyano | cyano |
| nitro | cyano |
| ethoxy | nitro |
| chloro | methylsulphonyl |

A preferred acylanilide of the invention has the formula stated above wherein $R^1$ and $R^2$, which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, $R^3$ and $R^4$ are both hydrogen, $R^5$ is hydroxy, $R^6$ is methyl or trifluoromethyl, $A^1$ is methylene, ethylene, trimethylene or tetramethylene and $R^7$ is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, methylthio, methylsulphinyl or methylsulphonyl substitutent.

A further preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, progestational, antiprogestational or both progestational and antiprogestational properties, has the formula stated above wherein $R^1$ is cyano, fluoro, hydrogen, ethoxy, methylsulphonyl or trifluoromethyl, wherein $R^2$ is cyano or nitro, wherein $R^3$ and $R^4$ are both hydrogen and $R^5$ is hydroxy, wherein $R^6$ is trifluoromethyl, wherein $A^1$ is methylene, ethylene, trimethylene or tetramethylene and wherein $R^7$ is phenyl which is unsubstituted or bears one substituent selected from fluoro, chloro and methyl.

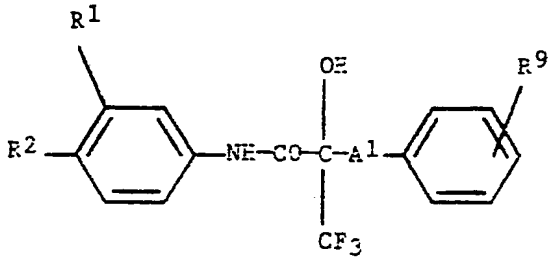
An especially preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, progestational or both progestational and antiprogestational properties, has the formula:-



wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2-F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3-F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | Cl | $-CH_2-$ | 3-Cl |
| Cl | CN | $-CH_2-$ | 3-Cl |
| Cl | CN | $-CH_2-$ | 4-Cl |
| Cl | CN | $-CH_2-$ | 3-F |
| $C_2H_5O$ | $NO_2$ | $-CH_2-$ | H |
| $CH_3SO_2$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-(CH_2)_4-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-F |

A further especially preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, antiprogestational or both antiprogestational and progestational properties, has the formula:-




wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

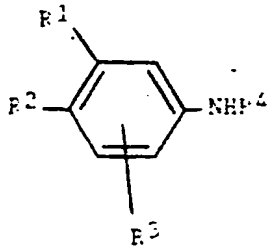
| $R^1$ | $R^2$ | $A^1$ | $R^3$ |
|---|---|---|---|
| Cl | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | 2—Cl |
| $CF_3$ | CN | $-CH_2-$ | 2—F |
| $CF_3$ | CN | $-CH_2-$ | 3—F |
| $CF_3$ | CN | $-CH_2-$ | 4—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3—F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2—Cl |
| Cl | CN | $-CH_2-$ | 4—Cl |
| Cl | CN | $-CH_2-$ | 2—F |
| Cl | CN | $-CH_2-$ | 3—F |
| Cl | CN | $-CH_2-$ | 4—F |
| F | CN | $-CH_2-$ | H |
| F | CN | $-CH_2-$ | 4—F |
| CN | CN | $-CH_2-$ | H |
| H | CN | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | 2—Cl |
| $CF_3$ | $NO_2$ | $-(CH_2)_3-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—F |

Specific acylanilides of the invention are hereinafter described in the Examples.

Particularly active compounds are 3-chloro-4-cyano-N-(2-hydroxy-3-p-methanesulphonylphenyl-2-trifluoromethylpropionyl)aniline;
3-chloro-4-cyano-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-3-trifluoromelthyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline;
4-nitro-3-triluoromethyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-N-(2-hydroxy-2-trifluoromethyl-4-phenylbutyryl)aniline;
4-nitro-3-trifluoromethyl-N-(3-o-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-m-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline or
4-cyano-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

A preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:-

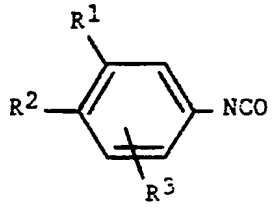


wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above, with an acid of the formula:-
$HO_2C\text{-}CR^5R^6\text{-}A^1\text{-}R^7$
wherein $R^5$, $R^6$, $R^7$ and $A^1$ have the meanings stated above, or with a reactive derivative of said acid.

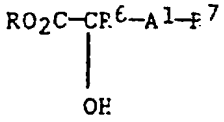
A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester.

Preferably the reaction is carried out in N,N-dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

An acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:-

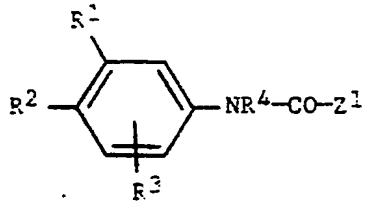


wherein $R^1$, $R^2$ and $R^3$ have the meanings stated above, with an ester of the formula:-

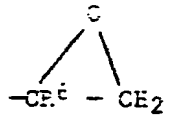


wherein $R^6$, $R^7$ and $A^1$ have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

An acylanilide of the invention wherein $R^7$ is heterocyclic and $A^1$ is methylene may be prepared by the reaction of an epoxide of the formula:-



wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above and wherein $Z^1$ has the formula:-



wherein $R^6$ has the meaning stated above, with a heterocycle or a reactive derivative thereof of the formula $R^7$-M wherein $R^7$ has the meaning stated immediately above and M is a metal radical. The reaction is preferably carried out in an inert diluent or solvent, for example diethyl ether or tetrahydrofuran at or near laboratory temperature, for example at between 0°C and 50°C.

The epoxide used as starting material may be obtained by the epoxidation, for example with a peracid, of the corresponding unsaturated acylanilide.

A suitable reactive derivative of a heterocycle of the formula $R^7$-M is, for example, an alkali metal salt of the heterocycle, for example the lithium or sodium salt, which may be prepared by the reaction of the heterocycle with, for example, an alkali metal alkyl, for example butyllithium.

The last-mentioned reaction is preferably carried out in an inert solvent, for example diethyl ether or tetrahydrofuran, at a low temperature, for example at between -30° and -80°C.

An acylanilide of the invention wherein $R^5$ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein $R^5$ is acyloxy, and an acylanilide of the invention wherein $R^5$ is hydroxy and $R^4$ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described above.

An acylanilide of the invention wherein $R^4$ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein $R^4$ is hydrogen.

An acylanilide of the invention wherein $R^5$ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein $R^5$ is hydroxy.

An oxazolidinedione of the invention, wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, may be prepared by the reaction of the corresponding acylanilide wherein $R^4$ is hydrogen and $R^5$ is hydroxy with phosgene ($COCl_2$).

An acylanilide of the invention wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or sulphonyl compound is obtained. Thus oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with a peracid, for example m-chloroperbenzoic acid in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

A racemic acylanilide of the invention wherein $R^5$ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group $R^5$ with an optically-active acid, for example (-)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallisation or, preferably, by flash-chromatography, and then hydrolysis of each separate ester to the alcohol.

As stated above, an acylanilide of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles of a mature male rat when administered orally for 4 successive days. An acylanilide of the invention may be used in the treatment of, for example, malignant or benign prostatic disease or of androgen dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

A preferred acylanilide of the invention is up to 10 times more active as an antiandrogen than the known, chemically-related antiandrogens flutamide and hydroxyflutamide. At a dose of an acylanilide of the invention which produces antiandrogenic activity in rats no symptoms of toxicity are apparent.

Some of the acylanilides of the invention also possess other hormonal or antihormonal activity, for example progestational or antiprogestational activity, or both such activities.

Any progestational activity possessed by an acylanilide of the invention can be demonstrated by its ability to promote glandular development in the endometrium of an oestrogen-primed immature rabbit, the standard Clauberg assay procedure. An acylanilide of the invention which possesses progestational activity may be used as a contraceptive, and in the treatment of menstrual disorders, such as dysmemorrhea,

dysfunctional bleeding and premenstrual tension, and in the treatment of hormone dependent tumours, especially those of the breast or endometrium. It may also be used for the synchronisation of oestrus and for the maintenance of early pregnancy in domestic animals such as cattle. At a dose of an acylanilide of the invention which produces progestational activity in rabbits no symptoms of toxicity are apparent.

Any antiprogestational activity possessed by an acylanilide of the invention can be demonstrated by its ability to terminate by day 16 the pregnancy of a mature female rat when administered subcutaneously twice on day 9 and once on day 10 of the pregnancy. An acylanilide of the invention which possesses antiprogestational activity may be used as a contraceptive, and in the treatment of menstrual disorders, such as dysmenorrhea, dysfunctional bleeding and premenstrual tension, and in the treatment of hormone dependent tumours, especially those of the breast or endometrium. At a dose of an acylanilide of the invention which produces antiprogestational activity in rats no symptoms of toxicity are apparent.

The acylanilide of the invention may be administered to a warm blooded animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration or be in the form of a suppository for anal or vaginal administration.

The composition may additionally contain one or more drugs selected from anti-oestrogens, for example tamoxifen; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide.

The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:-

Example 1

Thionyl chloride (0.73 ml.) was added to a stirred solution of 2-hydroxy-3-phenyl-2-trifluoromelthyl-propionic acid (2.34 g.) in N,N-dimethylacetamide (40 ml.) which was cooled to -15°C., at such a rate that that temperature was maintained, and the mixture was stirred at that temperature for 15 minutes. 3-Chloro-4-cyanoaniline (1.5 g.) was added, the mixture was stirred at -15°C. for 15 minutes and then at laboratory temperature for 15 hours, and was then poured into water (800 ml.). The mixture was extracted six times with diethyl ether (80 ml. each time) and the combined extracts were washed successively (50 ml. portions each time) twice with aqueous 2N-hydrochloric acid, once with saturated aqueous sodium chloride solution, twice with saturated aqueous sodium bicarbonate solution, and again once with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80°C.) as eluant. The product was crystallised from toluene and there was thus obtained 3-chloro-4-cyano-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline, m.p. 153-154°C.

The 2-hydroxy-3-phenyl-2-trifluoromethylpropionic acid used as starting material was prepared as follows:-

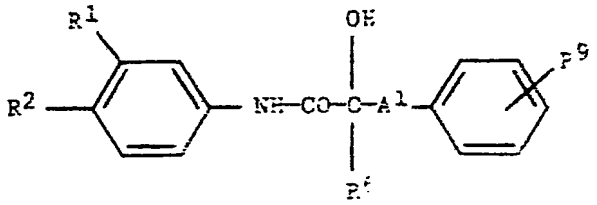
1,1,1-Trifluoro-3-phenylpropan-2-one (8.2 g, obtained by the process described in the Journal of Organic Chemistry, 1967, 32, 1316) was added dropwise to a cooled stirred solution of potassium cyanide (3.2 g.) in water (12 ml.) at such a rate that the temperature of the mixture was maintained at between 0° and 5°C. A 4:1 v/v mixture of water and concentrated sulphuric acid (60 ml.) was added at such a rate to maintain the above temperature, and the mixture was then stirred at laboratory temperature for 15 hours and then extracted three times with diethyl ether (20 ml. each time). The combined extracts were washed three times with water (25 ml. each time), dried overmagnesium sulphate and evaporated to dryness under reduced pressure.

A mixture of the cyanhydrin thus obtained (3.0 g.), concentrated aqueous hydrochloric acid (24 ml.) and acetic acid (6 ml.) was heated in a sealed tube at 110°C. for 6 hours, cooled and poured onto ice. The aqueous mixture was extracted four times with diethyl ether (25 ml. each time) and the combined ethereal solutions were extracted twice with saturated aqueous sodium bicarbonate solution (40 ml. each time). The

combined extracts were acidified with aqueous hydrochloric acid and then extracted twice with diethyl ether (40 ml. each time). The combined extracts were dried over magnesium sulphate and evaporated to dryness and the residue was crystallised from cyclohexane. There was thus obtained 2-hydroxy-3-phenyl-2-trifluoromethylpropionic acid, m.p. 123-124°C.

Example 2

The process described in Example 1 was repeated except that the appropriate aniline and the appropriate 2-hydroxy-phenylalkanoic acid were used as starting materials. There were thus obtained the compounds described in the following table:-



| $R^1$ | $R^2$ | $R^5$ | $A^1$ | $R^9$ | m.p. (°C.) |
|---|---|---|---|---|---|
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | — | 168–170 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 2–Cl | 104–105 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 3–Cl | 144–145 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–Cl | 182–184 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 2–F | 139–141 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 3–F | 146–149 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–F | 161–163 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–$SCH_3$ | (oil) |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | — | 119–121 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–$CH_3$ | 164–166 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2–Cl | 106–107 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 3–Cl | 161 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–Cl | 172–174 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2,6–diCl | 96–98 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2–F | 122–123 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 3–F | 175–176 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–F | 139–140 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–OH | 172–173 |

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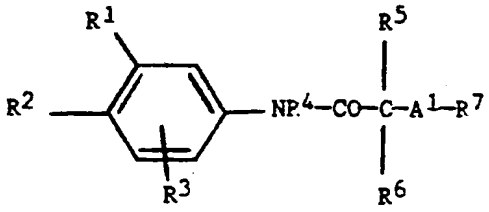
## (54) Substituted anilides having antiandrogenic properties.

(57) An acylanilide of the formula:-



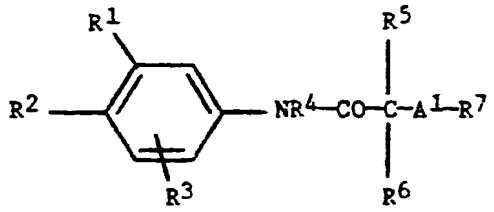
wherein $R^1$ or $R^2$ which may be the same or different, each is an electron-withdrawing substituent, alkylthio or phenylthio or $R^1$ is hydrogen, alkyl or alkoxy;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl, or is joined to $R^5$ as stated below:
wherein $R^5$ is hydrogen, hydroxy, alkoxy or acyloxy, or is joined to $R^4$ to form an oxycarbonyl group;
wherein $R^6$ is alkyl or halogenoalkyl, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene, alkenylene or alkynylene;
wherein $A^2$ is alkylene, alkenylene or alkynylene;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl, substituted phenyl, naphthyl or 5-or 6-membered saturated or unsaturated heterocyclic.
The compounds possess antiandrogenic properties and some of the compounds also possess progestational or antiprogestational activity.

EP 0 253 503 A2

# AMIDE DERIVATIVES

This invention relates to new amide derivatives and more particularly it relates to novel acylanilides which possess antiandrogenic properties.

According to the invention there is provided an acylanilide of the formula:



wherein $R^1$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^2$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to $R^5$ as stated below;
wherein $R^5$ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to $R^4$ to form an oxycarbonyl group such that together with the -N-CO-C-part of the molecule it forms an oxazolidinedione group;
wherein $R^6$ is alkyl or halogenoalkyl each of up to 4 carbon atoms, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms; wherein $A^2$ is alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; naphthyl; 5-or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents.

It will be observed that the acylanilide derivative of the invention possesses an asymmetric carbon atom, namely the carbon atom which bears the substituents $R^5$ and $R^6$, and it can therefore exist in racemic and optically-active forms. It is to be understood that this invention encompasses the racemic form of the acylanilide derivative and any optically-active form which possesses antiandrogenic activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any antiandrogenic activity present in any of these forms may be determined.

A suitable value for $R^1$ or $R^4$ when it is alkyl, or for an alkyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by alkyl is, for example, methyl or ethyl.

A suitable value for $R^1$ when it is alkoxy or for an alkoxy substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for $R^1$ or $R^2$ when it is alkanoyl, or for an alkanoyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl substituted by alkanoyl is, for example, formyl or acetyl.

A suitable value for $R^1$ or $R^2$ when it is alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl, or for such a substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic bearing such a substituent is, for example, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for $R^3$ when it is halogen, or for a halogen substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl or heterocyclic substituted by halogen, is fluoro, chloro, bromo or iodo.

$R^3$ is preferably hydrogen or chloro, especially hydrogen.

$R^4$ is preferably hydrogen.

A suitable value for an alkoxycarbonyl or N-alkylcarbamoyl substituent in $R^7$ or $R^8$ when $R^7$ or $R^8$ is phenyl bearing such a substituent is, for example, methoxycarbonyl, ethoxycarbonyl or N-methylcarbamoyl.

A suitable value for $R^5$ when it is alkoxy is, for example, methoxy, ethoxy, propyloxy, n-butyloxy or decyloxy.

A suitable value for $R^5$ when it is acyloxy is, for example, alkanoyl or aroyl each of up to 15 carbon atoms, for example acetoxy, propionyloxy, decanoyloxy, dodecanoyloxy or benzoyloxy.

$R^5$ is preferably hydroxy.

A suitable value for $R^6$ when it is alkyl or halogenoalkyl is, for example, methyl, ethyl, n-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, chloromethyl, dichloromethyl or trichloromethyl. $R^6$ is preferably trifluoromethyl.

A suitable value for $A^1$ when it is alkylene is, for example, methylene, ethylene, trimethylene or tetramethylene.

A suitable value for $A^2$ when it is alkylene is, for example, methylene, ethylene, trimethylene, tetramethylene.

1-methylethylene ($-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-$), 2-methylethylene ($-CH_2\underset{\displaystyle CH_3}{\underset{|}{CH}}-$) or

1,1,3-trimethylpropane-1,3-diyl ($-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2\underset{\displaystyle CH_3}{\underset{|}{CH}}-$).

A suitable value for $A^1$ or $A^2$ when it is alkenylene or alkynylene is, for example, vinylene (-CH = CH-), prop-1-enylene (-CH = CH-$CH_2$-), 2-methylprop-1-enylene

($-CH=\underset{\displaystyle CH_3}{\underset{|}{C}}-CH_2-$)

, ethynylene (-C≡C-), prop-1-ynylene (-C≡C-$CH_2$-) or prop-2-ynylene (-$CH_2$C≡C-).

A suitable value for $R^7$ or $R^8$ when it is heterocyclic is, for example, furyl, thienyl, pyrrolyl, pyridyl, imidazolyl, thiazolyl, thiadiazolyl, benzimidazolyl, indolyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or 1,2-dihydro-2-oxoquinolyl.

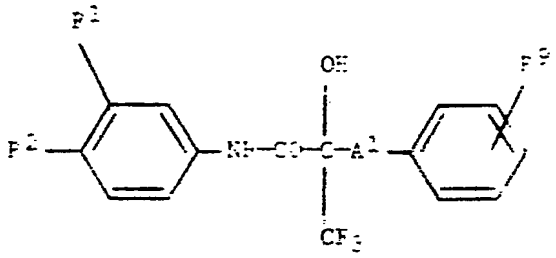
A preferred combination of values for $R^1$ and $R^2$ is as follows:-

| $R^1$ | $R^2$ |
|---|---|
| trifluoromethyl | nitro |
| trifluoromethyl | cyano |
| chloro | chloro |
| chloro | nitro |
| chloro | cyano |
| cyano | cyano |
| nitro | cyano |
| ethoxy | nitro |
| chloro | methylsulphonyl |

A preferred acylanilide of the invention has the formula stated above wherein $R^1$ and $R^2$, which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, $R^3$ and $R^4$ are both hydrogen, $R^5$ is hydroxy, $R^6$ is methyl or trifluoromethyl, $A^1$ is methylene, ethylene, trimethylene or tetramethylene and $R^7$ is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, methylthio, methylsulphinyl or methylsulphonyl substitutent.

A further preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, progestational, antiprogestational or both progestational and antiprogestational properties, has the formula stated above wherein $R^1$ is cyano, fluoro, hydrogen, ethoxy, methylsulphonyl or trifluoromethyl, wherein $R^2$ is cyano or nitro, wherein $R^3$ and $R^4$ are both hydrogen and $R^5$ is hydroxy, wherein $R^6$ is trifluoromethyl, wherein $A^1$ is methylene, ethylene, trimethylene or tetramethylene and wherein $R^7$ is phenyl which is unsubstituted or bears one substituent selected from fluoro, chloro and methyl.

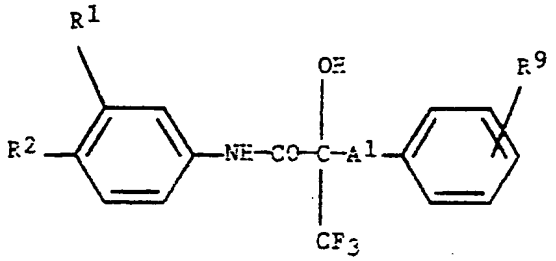
An especially preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, progestational or both progestational and antiprogestational properties, has the formula:-



wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3—F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | Cl | $-CH_2-$ | 3—Cl |
| Cl | CN | $-CH_2-$ | 3—Cl |
| Cl | Cl | $-CH_2-$ | 4—Cl |
| Cl | CN | $-CH_2-$ | 3—F |
| $C_2H_5O$ | $NO_2$ | $-CH_2-$ | H |
| $CH_3SO_2$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-(CH_2)_4-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—F |

A further especially preferred acylanilide of the invention, which possesses, in addition to antiandrogenic properties, antiprogestational or both antiprogestational and progestational properties, has the formula:-




wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

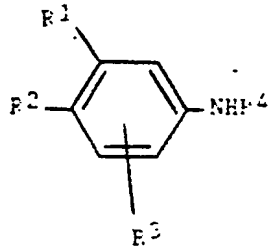
| $R^1$ | $R^2$ | $A^1$ | $R^3$ |
|---|---|---|---|
| Cl | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | 2—Cl |
| $CF_3$ | CN | $-CH_2-$ | 2—F |
| $CF_3$ | CN | $-CH_2-$ | 3—F |
| $CF_3$ | CN | $-CH_2-$ | 4—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3—F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2—Cl |
| Cl | CN | $-CH_2-$ | 4—Cl |
| Cl | CN | $-CH_2-$ | 2—F |
| Cl | CN | $-CH_2-$ | 3—F |
| Cl | CN | $-CH_2-$ | 4—F |
| F | CN | $-CH_2-$ | H |
| F | CN | $-CH_2-$ | 4—F |
| CN | CN | $-CH_2-$ | H |
| H | CN | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | 2—Cl |
| $CF_3$ | $NO_2$ | $-(CH_2)_3-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—F |

Specific acylanilides of the invention are hereinafter described in the Examples.

Particularly active compounds are 3-chloro-4-cyano-N-(2-hydroxy-3-p-methanesulphonylphenyl-2-trifluoromethylpropionyl)aniline;
3-chloro-4-cyano-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-3-trifluoromelthyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline;
4-nitro-3-triluoromethyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-cyano-N-(2-hydroxy-2-trifluoromethyl-4-phenylbutyryl)aniline;
4-nitro-3-trifluoromethyl-N-(3-o-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline;
4-nitro-3-trifluoromethyl-N-(3-m-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline or
4-cyano-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

A preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:-

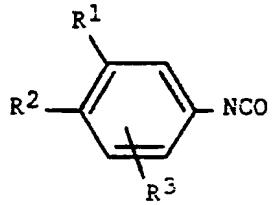


wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above, with an acid of the formula:-
$HO_2C-CR^5R^6-A^1-R^7$
wherein $R^5$, $R^6$, $R^7$ and $A^1$ have the meanings stated above, or with a reactive derivative of said acid.

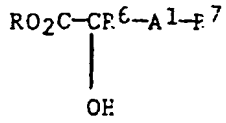
A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester.

Preferably the reaction is carried out in N,N-dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

An acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:-

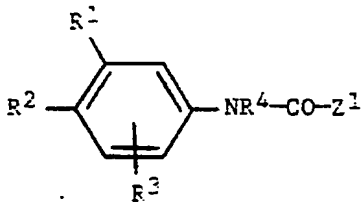


wherein $R^1$, $R^2$ and $R^3$ have the meanings stated above, with an ester of the formula:-

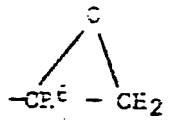


wherein $R^6$, $R^7$ and $A^1$ have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

An acylanilide of the invention wherein $R^7$ is heterocyclic and $A^1$ is methylene may be prepared by the reaction of an epoxide of the formula:-



wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above and wherein $Z^1$ has the formula:-



wherein $R^6$ has the meaning stated above, with a heterocycle or a reactive derivative thereof of the formula $R^7$-M wherein $R^7$ has the meaning stated immediately above and M is a metal radical. The reaction is preferably carried out in an inert diluent or solvent, for example diethyl ether or tetrahydrofuran at or near laboratory temperature, for example at between 0°C and 50°C.

The epoxide used as starting material may be obtained by the epoxidation, for example with a peracid, of the corresponding unsaturated acylanilide.

A suitable reactive derivative of a heterocycle of the formula $R^7$-M is, for example, an alkali metal salt of the heterocycle, for example the lithium or sodium salt, which may be prepared by the reaction of the heterocycle with, for example, an alkali metal alkyl, for example butyllithium.

The last-mentioned reaction is preferably carried out in an inert solvent, for example diethyl ether or tetrahydrofuran, at a low temperature, for example at between -30° and -80°C.

An acylanilide of the invention wherein $R^5$ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein $R^5$ is acyloxy, and an acylanilide of the invention wherein $R^5$ is hydroxy and $R^4$ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described above.

An acylanilide of the invention wherein $R^4$ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein $R^4$ is hydrogen.

An acylanilide of the invention wherein $R^5$ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein $R^5$ is hydroxy.

An oxazolidinedione of the invention, wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, may be prepared by the reaction of the corresponding acylanilide wherein $R^4$ is hydrogen and $R^5$ is hydroxy with phosgene ($COCl_2$).

An acylanilide of the invention wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or sulphonyl compound is obtained. Thus oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with a peracid, for example m-chloroperbenzoic acid in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

A racemic acylanilide of the invention wherein $R^5$ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group $R^5$ with an optically-active acid, for example (-)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallisation or, preferably, by flash-chromatography, and then hydrolysis of each separate ester to the alcohol.

As stated above, an acylanilide of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles of a mature male rat when administered orally for 4 successive days. An acylanilide of the invention may be used in the treatment of, for example, malignant or benign prostatic disease or of androgen dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

A preferred acylanilide of the invention is up to 10 times more active as an antiandrogen than the known, chemically-related antiandrogens flutamide and hydroxyflutamide. At a dose of an acylanilide of the invention which produces antiandrogenic activity in rats no symptoms of toxicity are apparent.

Some of the acylanilides of the invention also possess other hormonal or antihormonal activity, for example progestational or antiprogestational activity, or both such activities.

Any progestational activity possessed by an acylanilide of the invention can be demonstrated by its ability to promote glandular development in the endometrium of an oestrogen-primed immature rabbit, the standard Clauberg assay procedure. An acylanilide of the invention which possesses progestational activity may be used as a contraceptive, and in the treatment of menstrual disorders, such as dysmenorrhea,

dysfunctional bleeding and premenstrual tension, and in the treatment of hormone dependent tumours, especially those of the breast or endometrium. It may also be used for the synchronisation of oestrus and for the maintenance of early pregnancy in domestic animals such as cattle. At a dose of an acylanilide of the invention which produces progestational activity in rabbits no symptoms of toxicity are apparent.

Any antiprogestational activity possessed by an acylanilide of the invention can be demonstrated by its ability to terminate by day 16 the pregnancy of a mature female rat when administered subcutaneously twice on day 9 and once on day 10 of the pregnancy. An acylanilide of the invention which possesses antiprogestational activity may be used as a contraceptive, and in the treatment of menstrual disorders, such as dysmenorrhea, dysfunctional bleeding and premenstrual tension, and in the treatment of hormone dependent tumours, especially those of the breast or endometrium. At a dose of an acylanilide of the invention which produces antiprogestational activity in rats no symptoms of toxicity are apparent.

The acylanilide of the invention may be administered to a warm blooded animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration or be in the form of a suppository for anal or vaginal administration.

The composition may additionally contain one or more drugs selected from anti-oestrogens, for example tamoxifen; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide.

The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:-

Example 1

Thionyl chloride (0.73 ml.) was added to a stirred solution of 2-hydroxy-3-phenyl-2-trifluoromelthyl-propionic acid (2.34 g.) in N ,N-dimethylacetamide (40 ml.) which was cooled to -15°C., at such a rate that that temperature was maintained, and the mixture was stirred at that temperature for 15 minutes. 3-Chloro-4-cyanoaniline (1.5 g.) was added, the mixture was stirred at -15°C. for 15 minutes and then at laboratory temperature for 15 hours, and was then poured into water (800 ml.). The mixture was extracted six times with diethyl ether (80 ml. each time) and the combined extracts were washed successively (50 ml. portions each time) twice with aqueous 2N-hydrochloric acid, once with saturated aqueous sodium chloride solution, twice with saturated aqueous sodium bicarbonate solution, and again once with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80°C.) as eluant. The product was crystallised from toluene and there was thus obtained 3-chloro-4-cyano-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline, m.p. 153-154°C.

The 2-hydroxy-3-phenyl-2-trifluoromethylpropionic acid used as starting material was prepared as follows:-

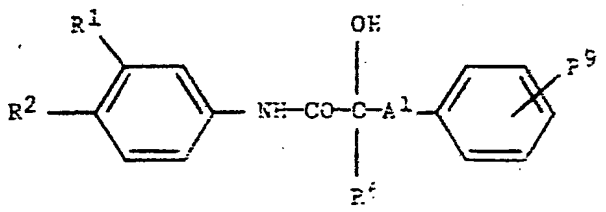
1,1,1-Trifluoro-3-phenylpropan-2-one (8.2 g, obtained by the process described in the Journal of Organic Chemistry, 1967, 32, 1316) was added dropwise to a cooled stirred solution of potassium cyanide (3.2 g.) in water (12 ml.) at such a rate that the temperature of the mixture was maintained at between 0° and 5°C. A 4:1 v/v mixture of water and concentrated sulphuric acid (60 ml.) was added at such a rate to maintain the above temperature, and the mixture was then stirred at laboratory temperature for 15 hours and then extracted three times with diethyl ether (20 ml. each time). The combined extracts were washed three times with water (25 ml. each time), dried overmagnesium sulphate and evaporated to dryness under reduced pressure.

A mixture of the cyanhydrin thus obtained (3.0 g.), concentrated aqueous hydrochloric acid (24 ml.) and acetic acid (6 ml.) was heated in a sealed tube at 110°C. for 6 hours, cooled and poured onto ice. The aqueous mixture was extracted four times with diethyl ether (25 ml. each time) and the combined ethereal solutions were extracted twice with saturated aqueous sodium bicarbonate solution (40 ml. each time). The

combined extracts were acidified with aqueous hydrochloric acid and then extracted twice with diethyl ether (40 ml. each time). The combined extracts were dried over magnesium sulphate and evaporated to dryness and the residue was crystallised from cyclohexane. There was thus obtained 2-hydroxy-3-phenyl-2-trifluoromethylpropionic acid, m.p. 123-124°C.

Example 2

The process described in Example 1 was repeated except that the appropriate aniline and the appropriate 2-hydroxy-phenylalkanoic acid were used as starting materials. There were thus obtained the compounds described in the following table:-



| $R^1$ | $R^2$ | $R^4$ | $A^1$ | $R^5$ | m.p. (°C.) |
|---|---|---|---|---|---|
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | — | 168–170 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 2–Cl | 104–105 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 3–Cl | 144–145 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–Cl | 182–184 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 2–F | 139–141 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 3–F | 148–149 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–F | 161–163 |
| $CF_3$ | CN | $CF_3$ | $-CH_2-$ | 4–$SCH_3$ | (oil) |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | — | 119–121 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–$CH_3$ | 164–166 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2–Cl | 106–107 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 3–Cl | 161 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–Cl | 172–174 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2,6–diCl | 96–98 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 2–F | 122–123 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 3–F | 175–176 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–F | 139–140 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4–OH | 172–173 |

/Continued...

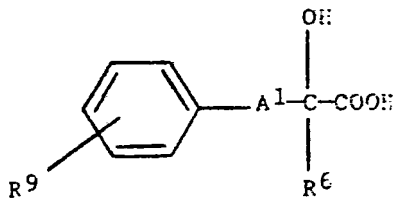
| $R^1$ | $R^2$ | $R^4$ | $A^1$ | $R^9$ | m.p. (°C.) |
|---|---|---|---|---|---|
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2-$ | 4-$SCH_3$ | 139–140 |
| Cl | Cl | $CF_3$ | $-CH_2-$ | – | 171–172* |
| Cl | $NO_2$ | $CF_3$ | $-CH_2-$ | – | 160–161 |
| Cl | $NO_2$ | $CF_3$ | $-CH_2-$ | 4-$SCH_3$ | (oil) |
| Cl | CN | $CF_3$ | $-CH_2-$ | 2-Cl | 109–111 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 3-Cl | 169–170 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 4-Cl | 174–175* |
| Cl | CN | $CF_3$ | $-CH_2-$ | 3,4-diCl | 180–181 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 2-F | 136–137 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 3-F | 152–153 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 4-F | 179–180 |
| Cl | CN | $CF_3$ | $-CH_2-$ | 4-$SCH_3$ | 143–144 |
| F | CN | $CF_3$ | $-CH_2-$ | – | 129–130 |
| F | CN | $CF_3$ | $-CH_2-$ | 4-F | 127–129 |
| CN | CN | $CF_3$ | $-CH_2-$ | – | 153–154 |
| H | CN | $CF_3$ | $-CH_2-$ | – | 163–164* |
| H | CN | $CF_3$ | $-CH_2-$ | 4-Cl | 174–176* |
| $CH_3$ | CN | $CF_3$ | $-CH_2-$ | – | 129–132* |
| H | $NO_2$ | $CF_3$ | $-CH_2-$ | – | 117–118 |
| H | $NO_2$ | $CF_3$ | $-CH_2-$ | 2-Cl | 92–93 |
| H | $NO_2$ | $CF_3$ | $-CH_2-$ | 4-Cl | 143–144 |
| H | $NO_2$ | $CF_3$ | $-CH_2-$ | 4-F | 119–121 |
| $C_2H_5O$ | $NO_2$ | $CF_3$ | $-CH_2-$ | – | 114–115 |
| Cl | $CH_3S$ | $CF_3$ | $-CH_2-$ | – | 185–186 |
| Cl | $CH_3SO_2$ | $CF_3$ | $-CH_2-$ | – | 175–176 |
| H | $CH_3SO_2$ | $CF_3$ | $-CH_2-$ | – | 200–201* |
| $CH_3S$ | CN | $CF_3$ | $-CH_2-$ | – | 169–172 |
| $CH_3SO_2$ | $NO_2$ | $CF_3$ | $-CH_2-$ | – | 192–194 |
| $C_6H_5S$ | $NO_2$ | $CF_3$ | $-CH_2-$ | – | 167–169 |
| $CF_3$ | $NO_2$ | $CH_3$ | $-CH_2-$ | – | 90–92 |
| $CF_3$ | CN | $CH_3$ | $-CH_2-$ | – | 134–135 |
| Cl | $NO_2$ | $CH_3$ | $-CH_2-$ | – | 132–134 |

/Continued...

| $R^1$ | $R^2$ | $R^6$ | $A^1$ | $R^9$ | m.p. (°C.) |
|---|---|---|---|---|---|
| $CF_3$ | $NO_2$ | $CH_2Cl$ | $-CH_2-$ | — | 80–82 |
| $CF_3$ | $NO_2$ | $CH_2C_6H_5$ | $-CH_2-$ | | 130–131 |
| $CF_3$ | $NO_2$ | 2-Thienyl | $-CH_2-$ | — | 118–121* |
| $CF_3$ | $NO_2$ | $CF_3$ | $-CH_2CH_2-$ | — | 131–132 |
| $CF_3$ | CN | $CF_3$ | $-CH_2CH_2-$ | — | 124–125 |
| Cl | Cl | $CF_3$ | $-CH_2CH_2-$ | — | 129–130* |
| Cl | CN | $CF_3$ | $-CH_2CH_2-$ | — | 154 |
| H | CN | $CF_3$ | $-CH_2CH_2-$ | — | 149–152* |
| H | $NO_2$ | $CF_3$ | $-CH_2CH_2-$ | — | 153–155* |
| $CF_3$ | $NO_2$ | $CF_3$ | $-(CH_2)_2-$ | — | 121–122 |
| $CF_3$ | CN | $CF_3$ | $-(CH_2)_3-$ | — | 144–145 |
| Cl | $NO_2$ | $CF_3$ | $-(CH_2)_3-$ | — | 97–99 |
| Cl | CN | $CF_3$ | $-(CH_2)_3-$ | — | 119–120 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-(CH_2)_4-$ | — | 107 |
| $CF_3$ | $NO_2$ | $CF_3$ | $-(CH_2)_7-$ | — | 84–85 |

* The chromatographic purification step was omitted as the product crystallised directly upon isolation.

All the anilines used as starting materials are known compounds. The 2-hydroxy-phenylalkanoic acids were obtained by a similar process to that described in the second part of Example 1 from the appropriate arylalkanone cyanhydrin. Those acids which are novel and which were characterised by melting point are described in the following table:-



| $R^5$ | $A^1$ | $R^6$ | m.p. (°C.) |
|---|---|---|---|
| 2-Cl | $-CH_2-$ | $CF_3$ | 123-125 |
| 3-Cl | $-CH_2-$ | $CF_3$ | 106-109 |
| 4-Cl | $-CH_2-$ | $CF_3$ | 121-124 |
| 4-$CH_3$ | $-CH_2-$ | $CF_3$ | 111-113 |
| 3,4-diCl | $-CH_2-$ | $CF_3$ | 104-107 |
| 3,5-diCl | $-CH_2-$ | $CF_3$ | 98-101 |
| 2-F | $-CH_2-$ | $CF_3$ | 107-109 |
| 3-F | $-CH_2-$ | $CF_3$ | 103-104 |
| 4-F | $-CH_2-$ | $CF_3$ | 108-111 |
| 4-OH | $-CH_2-$ | $CF_3$ | 176-177 |
| 4-$CH_3S$ | $-CH_2-$ | $CF_3$ | 125-126 |
| - | $-CH_2-$ | $CH_2Cl$ | 125-129 |
| - | $-CH_2-$ | 2-thienyl | 140-142 |
| - | $-CH_2CH_2-$ | $CF_3$ | 104-105 |
| - | $-(CH_2)_3-$ | $CF_3$ | 95-96 |
| - | $-(CH_2)_4-$ | $CF_3$ | 86-88 |

The arylalkanones were prepared from the appropriate Grignard reagent by the general process described in the Journal of Organic Chemistry, 1967, 32, 1316. Those which are novel and which were characterised by boiling points are described in the following table:-

| $R^9$ | $A^1$ | $R^6$ | b.p. (°C./mm.Hg.) |
|---|---|---|---|
| 2-Cl | $-CH_2-$ | $CF_3$ | 9[illegible]–93/15 |
| 3-Cl | $-CH_2-$ | $CF_3$ | 87–89/15 |
| 4-Cl | $-CH_2-$ | $CF_3$ | 95–98/15 |
| 4-$CH_3$ | $-CH_2-$ | $CF_3$ | 7[illegible]/15 |
| 3,4-diCl | $-CH_2-$ | $CF_3$ | 120–123/10 |
| 2,6-diCl | $-CH_2-$ | $CF_3$ | 90–95/1.5 |
| 2-F | $-CH_2-$ | $CF_3$ | 44–45/[illegible] |
| 3-F | $-CH_2-$ | $CF_3$ | 60–62/[illegible] |
| 4-F | $-CH_2-$ | $CF_3$ | 60–62/5 |
| 4-$CH_3S$ | $-CH_2-$ | $CF_3$ | 10[illegible]–10[illegible]/[illegible] |
| – | $-CH_2CH_2-$ | $CF_3$ | 8[illegible]–8[illegible]/[illegible] |
| – | $-(CH_2)_3-$ | $CF_3$ | 95–100 [illegible] |
| – | $-(CH_2)_4-$ | $CF_3$ | 10[illegible]–111/10 |
| – | $-(CH_2)_7-$ | $CF_3$ | 121–124/[illegible] |

Example 3

A solution of sodium metaperiodate (0.6 g.) in water (10 ml.) was added to a stirred solution of 4-cyano-3-methylthio-N-(2-hydroxy-3-phenyl-2-trifluoro-methylpropionyl)aniline (0.9 g. ) in methanol (75 ml.) and the reaction mixture was stirred at laboratory temperature for 24 hours and then filtered. The filtrate was shaken with 10% w/v aqueous sodium thiosulphate solution (25 ml.), the mixture was filtered and the filtrate was extracted three times with ethyl acetate (25 ml. each time). The combined extracts were dried over magnesium sulphate and evaporated to dryness under reduced pressure, and the residue was crystallised from toluene. There was thus obtained 4-cyano-3-methylsulphinyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline, m.p. 92-97°C.

The process described above was repeated using 4-nitro-3-trifluoromethyl-N-(2-hydroxy-3-p-methylthiophenyl-2-trifluoromethylpropionyl)aniline as starting material, and there was thus obtained 4-nitro-3-trifluoromethyl-N-(2-hydroxy-3-p-methylsulphinylphenyl-2-trifluoromethylpropionyl)aniline, m.p. 193-196°C.

The process described above was repeated using 3-chloro-4-cyano-N-(2-hydroxy-3-p-methylthiophenyl)-2-trifluoromethylpropionyl)aniline as starting material, and there was thus obtained 3-chloro-4-cyano-N-(2-hydroxy-3-p-methylsulphinylphenyl-2-trifluoromelthylpropionyl)aniline, m.p. 210-213°C.

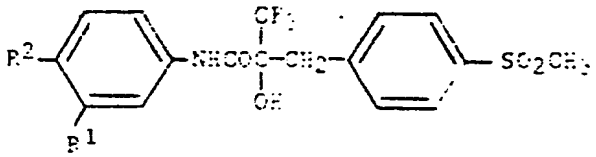
The process described above was repeated using 3-chloro-4-methylthio-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline as starting material, and there was thus obtained 3-chloro-4-methylsulphinyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline, m.p. 185-187°C.

Example 4

A solution of m-chloroperbenzoic acid (1.2 g.) in methylene chloride (70 ml.) was added dropwise to a stirred solution of 3-chloro-4-cyano-N-(2-hydroxy-3-p-methylthiophenyl-2-trifluoromethylpropionyl)aniline (1.1g.)in methylene chloride (180 ml.) and the mixture was stirred at laboratory temperature for 15 hours and then shaken with 10% w/v aqueous sodium sulphite solution (45 ml.). The methylene chloride phase was separated, washed three times with saturated aqueous sodium bicarbonate solution (25 ml. ech time)

and then with saturated sodium chloride solution (25 ml.), then filtered through phase-separating paper, dried and evaporated to dryness under reduced pressure. The residue was stirred with petroleum ether (b.p. 60-80°C.) and the mixture was filtered. There was thus obtained as solid residue 3-chloro-4-cyano-N-(2-hydroxy-3-methyl-sulphonylphenyl-2-trifluoromethylpropionyl)aniline, m.p. 204-205°C.

The process described above was repeated using the appropriate aniline as starting material and there were thus obtained the compounds described in the following table:-



| $R^1$ | $R^2$ | m.p. (°C.) |
|---|---|---|
| $CF_3$ | $NO_2$ | 204-205 |
| $CF_3$ | CN | 220-230 |
| Cl | $NO_2$ | 197-199 |

Example 5

A solution of racemic 4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)-aniline (6.5 g.) and (-)-camphanoyl chloride (4.8 g.) in pyridine (25 ml.) was heated at 95°C. for 3 hours and then poured into water (400 ml.), and the mixture was extracted three times with ethyl acetate (100 ml. each time). The combined extracts were washed twice with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (15 ml.) and the solution was flash-chromatographed on silica gel (Merck 9385; 450 g.) using methylene chloride as eluant. There were thus obtained the two diastereoisomers of 4-nitro-3-trifluoromethyl-N-[2-(-)-camphanoyloxy-3-p -fluorophenyl-3-trifluoromethylpropionyl]aniline, the less polar isomer having m.p. 142°C. and the more polar isomer having m.p.65-72°C.

A mixture of a solution of the less polar isomer (3.0g.) in methanol (20 ml.) and a solution of sodium hydroxide (0.2 g.) in water (3.5 ml.) was stirred at laboratory temperature for 30 minutes and the methanol was then removed by evaporation under reduced pressure. Water (40 ml.) was added and the mixture was extracted three times with ethyl acetate (25 ml. each time). The combined extracts were successively washed (25 ml. portions each time) twice with aqueous 2N-hydrochloric acid, twice with water and once with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue was stirred with petroleum ether (b.p. 60-80°C.) and the mixture was filtered. There was thus obtained as solid residue (+)-4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethyl-propionyl)aniline, m.p. 118-120°C., $[\alpha]_D^{25}$ = + 197.2 (C, 1%in methanol).

The process described in the preceding paragraph was repeated using the more polar isomer of the camphanoyl ester, and the hydrolysis product was crystallised from a 10:1 v/v mixture of petroleum ether (b.p. 60-80°C.) and toluene. There was thus obtained (-)-4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline, m.p. 105-107°C., $[\alpha]_D^{25}$ = -195.2 (C, 1% methanol).

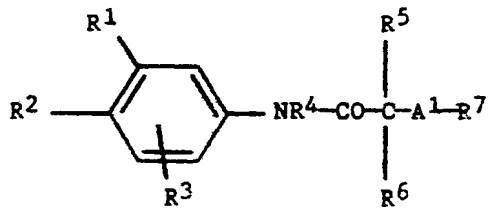
Example 6

A solution of 3,4-dichloro-N-(2,3-epoxy-2-methylpropionyl)aniline (1.23 g.) in diethyl ether (15 ml.) was added dropwise to a solution of 2-thienyllithium [prepared by the addition of 6.25 ml. of a 1.6 molar solution of butyllithium in hexane to a solution of thiophene (1.15 g.) in diethyl ether (15 ml.)] at such a rate that the temperature of the mixture did not rise above 30°C. The mixture was stirred at laboratory temperature for 1.5 hours and poured into water (50 ml.). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether (25 ml. each time). The combined extracts were washed with water and with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residual oil was purified by chromatography on silica gel using methylene chloride as eluant. There was thus obtained 3,4-dichloro-N-[2-hydroxy-2-methyl-3-(2-thienyl)-propionyl]aniline, m.p. 68-71°C.

The 3,4-dichloro-N-(2,3-epoxy-2-methylpropionyl)aniline used as starting material was prepared by the reaction of 3,4-dichloro-N-methacryloylaniline (prepared as described in the Journal of Organic Chemistry, 1963, 28, 2915) and m-chloroperbenzoic acid using the method described in the Journal of the Chemical Society, Chemical Communications, 1972, 64.

## Claims

1. An acylanilide of the formula:-

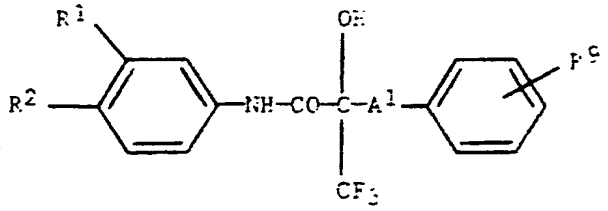


wherein $R^1$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^2$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to $R^5$ as stated below;
wherein $R^5$ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to $R^4$ to form an oxycarbonyl group such that together with the -N-CO-C-part of the molecule it forms an oxazolidinedione group;
wherein $R^6$ is alkyl or halogenoalkyl each of up to 4 carbon atoms, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms; wherein $A^2$ is alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; naphthyl; 5-or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy- or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents.

2. An acylanilide as claimed in claim 1, wherein $R^1$ and $R^2$, which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, $R^3$ and $R^4$ are both hydrogen, $R^5$ is hydroxy, $R^6$ is methyl or trifluoromethyl, $A^1$ is methylene, ethylene, trimethylene or tetramethylene and $R^7$ is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, methylthio, methylsulphinyl or melthylsulphonyl substitutent.

3. An acylanilide as claimed in claim 1, wherein $R^1$ is cyano, fluoro, hydrogen, ethoxy, methylsulphonyl or trifluoromethyl, wherein $R^2$ is cyano or nitro, wherein $R^3$ and $R^4$ are both hydrogen and $R^5$ is hydroxy, wherein $R^6$ is trifluoromethyl, wherein $A^1$ is methylene, ethylene, trimethylene or tetramethylene and wherein $R^7$ is phenyl which is unsubstituted or bears one substituent selected from fluoro, chloro and methyl.

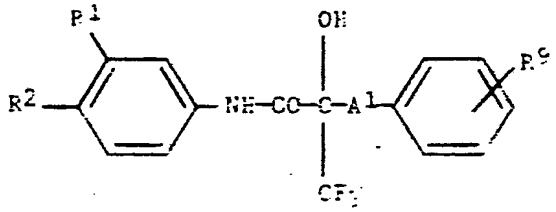
4. An acylanilide selected from the group of compounds of the formula:-



wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-$CH_3$ |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2-F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3-F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2-Cl |
| Cl | CN | $-CH_2-$ | 3-Cl |
| Cl | CN | $-CH_2-$ | 4-Cl |
| Cl | CN | $-CH_2-$ | 3-F |
| $C_2H_5O$ | $NO_2$ | $-CH_2-$ | H |
| $CH_3SO_2$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-(CH_2)_4-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-F |

5. An acylanilide selected from the group of compounds of the formula:-



wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| Cl | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | 2—Cl |
| $CF_3$ | CN | $-CH_2-$ | 2—F |
| $CF_3$ | CN | $-CH_2-$ | 3—F |
| $CF_3$ | CN | $-CH_2-$ | 4—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4—Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2—F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3—F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2—Cl |
| Cl | CN | $-CH_2-$ | 4—Cl |
| Cl | CN | $-CH_2-$ | 2—F |
| Cl | CN | $-CH_2-$ | 3—F |
| Cl | CN | $-CH_2-$ | 4—F |
| F | CN | $-CH_2-$ | H |

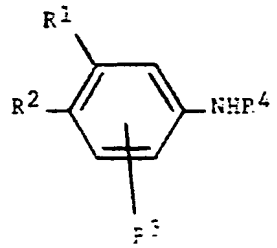
/Continued..

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| F | CN | $-CH_2-$ | 4-F |
| CN | CN | $-CH_2-$ | H |
| H | CN | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | 2-Cl |
| $CF_3$ | $NO_2$ | $-(CH_2)_3$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-F |

6. The compound 3-chloro-4-cyano-N-(2-hydroxy-3-p-methanesulphonylphenyl-2-trifluoromethylpropionyl)aniline; 3-chloro-4-cyano-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-cyano-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline; 4-nitro-3-trifluoromethyl-N-(2-hydroxy-3-phenyl-2-trifluoromethylpropionyl)aniline; 4-nitro-3-trifluoromethyl-N-(3-p-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-nitro-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-nitro-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-cyano-N-(2-hydroxy-2-trifluoromethyl-4-phenylbutyryl)aniline; 4-nitro-3-trifluoromethyl-N-(3-o-chlorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline; 4-nitro-3-trifluoromethyl-N-(3-m-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline or 4-cyano-3-trifluoromethyl-N-(3-p-fluorophenyl-2-hydroxy-2-trifluoromethylpropionyl)aniline.

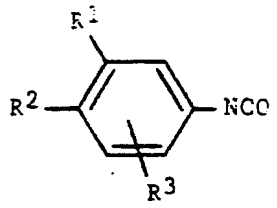
7. A process for the manufacture of an acylanilide claimed in claim 1 which comprises:-

(a) the reaction of an amine of the formula

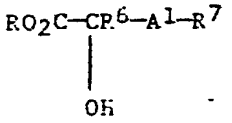


wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated in claim 1, with an acid of the formula:-
$HO_2C-CR^5R^6-A^1-R^7$
wherein $R^5$, $R^6$, $R^7$ and $A^1$ have the meanings stated in claim 1 or with a reactive derivative of said acid;

(b) for the manufacture of an acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, that is, an oxazolidinedione, the reaction of an isocyanate of the formula:-

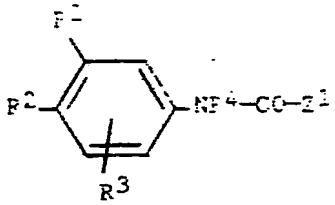


wherein $R^1$, $R^2$ and $R^3$ have the meanings stated in claim 1, with an ester of the formula:-

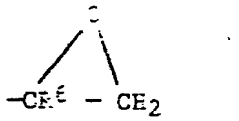


wherein $R^6$, $R^7$ and $A^1$ have the meanings stated in claim 1 and wherein R is alkyl of up to 6 carbon atoms;

(c) for the manufacture of an acylanilide of the invention wherein $R^7$ is heterocylic and $A^1$ is methylene, the reaction of an epoxide of the formula:-



wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated in claim 1 and wherein $Z^1$ has the formula:-



wherein $R^6$ has the meaning stated in claim 1, with a heterocycle or a reactive derivative thereof of the formula $R^7$-M wherein $R^7$ has the meaning stated immediately above and M is a metal radical;

(d) for the manufacture of an acylanilide of the invention wherein $R^5$ is hydroxy, the hydrolysis of the corresponding acylanilide wherein $R^5$ is acyloxy;

(e) for the manufacture of an acylanilide of the invention wherein $R^5$ is hydroxy and $R^4$ is hydrogen, the hydrolysis of the corresponding oxazolidinedione;

(f) for the manufacture of an acylanilide of the invention wherein $R^4$ is alkyl, the alkylation of the corresponding acylanilide wherein $R^4$ is hydrogen;

(g) for the manufacture of an acylanilide of the invention wherein $R^5$ is acyloxy, the acylation of the corresponding acylanilide wherein $R^5$ is hydroxy;

(h) for the manufacture of an acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, the reaction of the corresponding acylanilide wherein $R^4$ is hydrogen and $R^5$ is hydroxy with phosgene ($COCl_2$);

(i) for the manufacture of an acylanilide of the invention wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, the oxidation of the corresponding acylanilide wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylthio, perfluoroalkylthio or phenylthio, respectively; or

(j) for the separation into its optical isomers of an acylanilide of the invention wherein $R^5$ is hydroxy, the formation of an ester of the hydroxy group $R^5$ with an optically-active acid, the separation of the diastereoisomeric esters thus obtained, by fractional cystallisation or by flash-chromatography, and then the hydrolysis of each separate ester to the alcohol.

8. A pharmaceutical composition comprising an acylanilide as claimed in claim 1, together with a pharmaceutically acceptable diluent or carrier; the composition optionally containing one or more drugs selected from anti-oestrogens, progestins, inhibitors of gonodotrophin secretion, cytotoxic agents, antibiotics and anti-inflammatory agents.

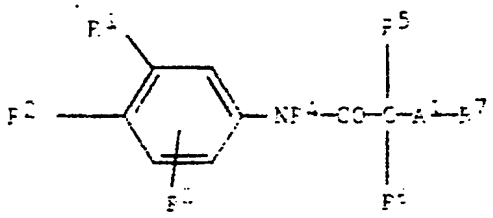
9. The use of an acylanilide as claimed in claim 1 for the manufacture of a medicament for producing an antiandrogenic effect in a warm-blooded animal.

10. The use of an acylanilide as claimed in claim 4 for the manufacture of a medicament for producing a progestational effect in a warm-blooded animal.

11. The use of an acylanilide as claimed in claim 5 for the manufacture of a medicament for producing an antiprogestational effect in a warm-blooded animal.

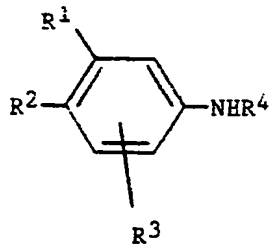
National Claims for Austria, Greece and Spain

1. A process for the manufacture of an acylanilide of the formula:-



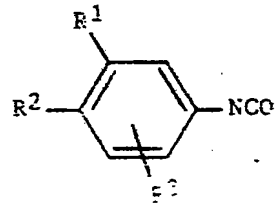
wherein $R^1$ ia cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^2$ is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
wherein $R^3$ is hydrogen or halogen;
wherein $R^4$ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to $R^5$ as stated below;
wherein $R^5$ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to $R^4$ to form an oxycarbonyl group such that together with the -N-CO-C-part of the molecule it forms an oxazolidinedione group;
wherein $R^6$ is alkyl or halogenoalkyl each of up to 4 carbon atoms, or has the formula $-R^8$ or $-A^2-R^8$;
wherein $A^1$ is straight-chain alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms; wherein $A^2$ is alkylene of up to 10 carbon atoms, or alkenylene or alkynylene each of 2 to 10 carbon atoms;
and wherein $R^7$ and $R^8$, which may be the same or different, each is selected from phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, hydroxy, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N -alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; naphthyl; 5-or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents, characterised by

(a) the reaction of an amine of the formula:-

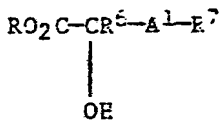


wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above, with an acid of the formula:-
$HO_2C-CR^5R^6-A^1-R^7$
wherein $R^5$, $R^6$, $R^7$ and $A^1$ have the meanings stated above, or with a reactive derivative of said acid, or

(b) for the manufacture of an acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, that is, an oxazolidinedione, the reaction of an isocyanate of the formula:-

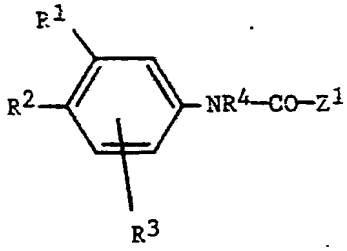


wherein $R^1$, $R^2$ and $R^3$ have the meanings state above, with an ester of the formula:-

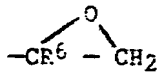


wherein $R^6$, $R^7$ and $A^1$ have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms; or

(C) for the manufacture of an acylanilide of the invention wherein $R^7$ is heterocyclic and $A^1$ is methylene, the reaction of an epoxide of the formula:-



wherein $R^1$, $R^2$, $R^3$ and $R^4$ have the meanings stated above and wherein $Z^1$ has the formula:-



wherein $R^6$ has the meaning stated above, with a heterocycle or a reactive derivative thereof of the formula $R^7$-M wherein $R^7$ has the meaning stated immediately above and M is a metal radical; or

(d) for the manufacture of an acylanilide of the invention wherein $R^5$ is hydroxy, the hydrolysis of the corresponding acylanilide wherein $R^5$ is acyloxy; or

(e) for the manufacture of an acylanilide of the invention wherein $R^5$ is hydroxy and $R^4$ is hydrogen, the hydrolysis of the corresponding oxazolidinedione; or

(f) for the manufacture of an acylanilide of the invention wherein $R^4$ is alkyl, the alkylation of the corresponding acylanilide wherein $R^4$ is hydrogen; or

(g) for the manufacture of an acylanilide of the invention wherein $R^5$ is acyloxy, the acylation of the corresponding acylanilide wherein $R^5$ is hydroxy; or

(h) for the manufacture of an acylanilide of the invention wherein $R^4$ and $R^5$ are joined together to form a carbonyl-oxy group, the reaction of the corresponding acylanilide wherein $R^4$ is hydrogen and $R^5$ is hydroxy with phosgene ($COCl_2$); or

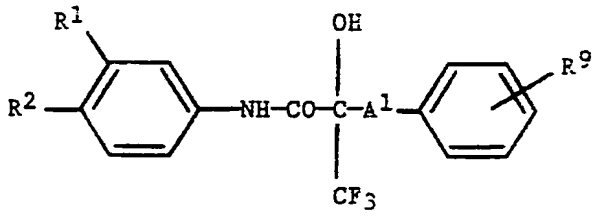
(i) for the manufacture of an acylanilide of the invention wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, the oxidation of the corresponding acylanilide wherein one or more of $R^1$, $R^2$ and a substituent in the phenyl or heterocyclic group $R^7$ or $R^8$ is alkylthio, perfluoroalkylthio or phenylthio, respectively, or

(j) for the separation into its optical isomers of an acylanilide of the invention wherein $R^5$ is hydroxy, the formation of an ester of the hydroxy group $R^5$ with an optically-active acid, the separation of the diastereoisomeric esters thus obtained, by fractional cystallisation or by flash-chromatography, and then the hydrolysis of each separate ester to the alcohol.

2. A process as claimed in clause (a), (d), (e), (i) or (j) of claim 1, wherein $R^1$ and $R^2$ which may be the same or different, each is cyano, nitro, trifluoromethyl, methylthio, methylsulphinyl, methylsulphonyl or chloro, $R^3$ and $R^4$ are both hydrogen, $R^5$ is hydroxy, $R^6$ is methyl or trifluoromethyl, $A^1$ is methylene, ethylene, trimethylene or tetramethylene and $R^7$ is phenyl which is unsubstituted or which bears one fluoro, chloro, hydroxy, methyl, methylthio, methylsulphinyl or methylsulphonyl substitutent.

3. A process as claimed in clause (a), (d), (e), (i) or (j) of claim 1, wherein $R^1$ is cyano, fluoro, hydrogen, ethoxy, methylsulphonyl or trifluoromethyl, wherein $R^2$ is cyano or nitro, wherein $R^3$ and $R^4$ are both hydrogen and $R^5$ is hydroxy, wherein $R^6$ is trifluoromethyl, wherein $A^1$ is methylene, ethylene, trimethylene or tetramethylene and wherein $R^7$ is phenyl which is unsubstituted or bears one substituent selected from fluoro, chloro and methyl.

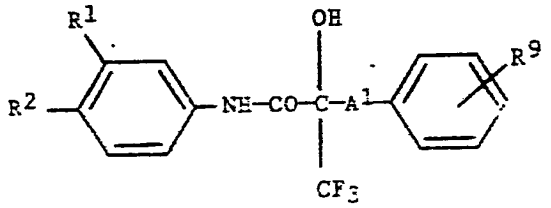
4. A process as claimed in clause (a), (d), (e), (i) or (j) of claim 1 for the manufacture of an acylanilide selected from the group of compounds of the formula:-




wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4–$CH_3$ |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2–Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3–Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4–Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2–F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3–F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2–Cl |
| Cl | CN | $-CH_2-$ | 3–Cl |
| Cl | CN | $-CH_2-$ | 4–Cl |
| Cl | CN | $-CH_2-$ | 3–F |
| $C_2H_5O$ | $NO_2$ | $-CH_2-$ | H |
| $CH_3SO_2$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-(CH_2)_4-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4–F |

5. A process as claimed in clause (a), (d), (e) or (j) of claim 1 for the manufacture of an acylanilide selected from the group of compounds of the formula:-



wherein the specific values of $R^1$, $R^2$, $A^1$ and $R^9$ are shown in the following table:-

| $R^1$ | $R^2$ | $A^1$ | $R^9$ |
|---|---|---|---|
| Cl | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | H |
| $CF_3$ | CN | $-CH_2-$ | 2-Cl |
| $CF_3$ | CN | $-CH_2-$ | 2-F |
| $CF_3$ | CN | $-CH_2-$ | 3-F |
| $CF_3$ | CN | $-CH_2-$ | 4-F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-Cl |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 2-F |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 3-F |
| Cl | $NO_2$ | $-CH_2-$ | H |
| Cl | CN | $-CH_2-$ | 2-Cl |
| Cl | CN | $-CH_2-$ | 4-Cl |
| Cl | CN | $-CH_2-$ | 2-F |
| Cl | CN | $-CH_2-$ | 3-F |
| Cl | CN | $-CH_2-$ | 4-F |
| F | CN | $-CH_2-$ | H |
| H | CN | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | H |
| H | $NO_2$ | $-CH_2-$ | 2-Cl |
| $CF_3$ | $NO_2$ | $-(CH_2)_3-$ | H |
| $CF_3$ | $NO_2$ | $-CH_2-$ | 4-F |